09/720,576

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GAGALA, Bruce, M.
Leydig, Voit & Mayer, Ltd.
Suite 4900
Two Prudential Plaza
180 North Stetson
Chicago, IL 60601-6780
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 01 February 2001 (01.02.01)	
Applicant's or agent's file reference 201449	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/14119	**International filing date** (day/month/year) 23 June 1999 (23.06.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	JP	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
MITSUYA, Hiroaki 4601 North Park Avenue Apartment 1010 Chevy Chase, MD 20815 United States of America	JP	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Additional applicant/inventor for US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

09/720276

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rul s 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
201449		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 14119	23/06/1999	23/06/1998
Applicant		
THE UNITED STATES OF AMERICA, represented by THE S		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 14119

Box III TEXT OF THE ABSTRACT (C ntinuation of item 5 of the first sh et)

The abstract is changed as follows:
Line 10:delete line 10 until the end of the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/14119

Box I Observations wher certain claims were found unsearchable (Continuati n of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1-45
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-62

    1. Claims: 1-46

    Assays for determining evolutionary response of a viral protease to a protease inhibitor and methods of administering compounds identified using this assay, and afluorigenic assay for measuring anti-Hiv protease activity of a protease inhibitor.

    2. Claims: 47-62

    Method of preventing the development of drug resistance in an HIV infected mammal by administering compounds that inhibit development of drug-resistance.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 47-62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Claims Nos.: 20-45

Rule 39.1(iv) PCT- Method of treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 1-45

The claims so lack support, and the application so lacks disclosure, that ameaningful search over the whole of the claimed scope is impossible. Present claims 1-45 relate to a large number of possible assays. In fact, the claims contain so many options, variables, that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely for an assay for determination of the activity of a viral protease of a mutant HIV-1 or HIV-2 in relation to its predecessor comprising obtaining a predecessor, determining the activity of the protease of said predecessor in the presence of a protease inhibitor, determining the activity of said protease inhibitor and comparing the two protease activities.(i.e. the first subject-matter of claim 12 when referring back to claims 1 via claim 5).

The description does not provide a proper support within the meaning of Article 5 and 6 PCT for any other embodiment covered by claims 1-45.

Morever claims 20-45 refer to therapeutic compounds which are not characterised by any technical feature which would allow the formulation of a search for these claims or which would allow a meaningful comparison with methods of the state of the art.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/14119

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D493/04 C07D491/04 C07D495/04 A61K31/34 C12Q1/37
A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 766 842 A (HEEFNER DONALD L ET AL.) 16 June 1998 (1998-06-16) column 1, line 12 - line 40; claims 1,20 ---	1,5,12
X	KLABE, RONALD M. ET AL.: ""Resistance to HIV Protease Inhibitors: A Comparison of enzyme Inhibition and antiviral Potency"" BIOCHEMISTRY, vol. 37, no. 24, 1998, pages 8735-8742, XP002126126 Abstract --- -/--	1,5,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2000	13. 6. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BORMAN, ANDREW M. ET AL: "Resistance of human immunodeficiency virus type 1 to protease inhibitors: selection of resistance mutations in the presence and absence of the drug" J. GEN. VIROL. , vol. 77, no. 3, 1996, pages 419-426, XP002126127 abstract	1,5,12
X	MARTINEZ-PICADO, JAVIER ET AL: "Replicative fitness of protease inhibitor-resistant mutants of human immunodeficiency virus type 1" J. VIROL., vol. 73, no. 5, 1999, pages 3744-3752, XP002126128 abstract	1,5,12
A	WO 90 09191 A (SCHRAMM WOLFGANG; SCHRAMM HANS) 23 August 1990 (1990-08-23) the whole document	46
A	GB 2 276 621 A (MERCK & CO INC.) 5 October 1994 (1994-10-05) the whole document	46
A	WO 97 19055 A (NOVARTIS AG) 29 May 1997 (1997-05-29) page 1 -page 14	47-62
A	WO 96 28463 A (G. D. DEARLE & CO.) 19 September 1996 (1996-09-19) page 4 -page 14, line 12 page 145 -page 189	47-62
A	WO 95 06030 A (G. D. SEARLE & CO.) 2 March 1995 (1995-03-02) page 4 -page 18, paragraph 21 page 192 -page 212	47-62
A	WO 94 14793 A (G. D. SEARLE & CO.) 7 July 1994 (1994-07-07) page 3, line 10 -page 13	47-62
A	US 5 753 660 A (JAMES A. SIKORSKI ET AL.) 19 May 1998 (1998-05-19) the whole document	47-62
A	US 5 728 718 A (RAMNARAYAN S. RANDAD ET AL.) 17 March 1998 (1998-03-17) cited in the application the whole document	47-62

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/14119

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 723 490 A (ROGER D. TUNG) 3 March 1998 (1998-03-03) the whole document	47-62
A	US 5 705 500 A (DANIEL P. GETMAN ET AL.) 6 January 1998 (1998-01-06) the whole document	47-62
A	US 5 703 076 A (JOHN J. TALLEY) 30 December 1997 (1997-12-30) cited in the application the whole document	47-62
A	US 5 502 060 A (WAYNE J. THOMPSON) 26 March 1996 (1996-03-26) cited in the application the whole document	47-62

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/14119

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		CA 2199805 A	21-03-1996
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INTERNATIONAL SEARCH REPORT

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International Application No
PCT/US 99/14119

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/14119

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/14119

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ES 2059293 T	16-11-1994
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09/720276 15

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
201449		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/14119	23/06/1999	23/06/1998
International Patent Classification (IPC) or national classification and IPC		
C12Q1/00		
Applicant		
THE UNITED STATES OF AMERICA, represented by THE S		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the International application

Date of submission of the demand	Date of completion of this report
21/01/2000	20.10.2000
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Bradbrook, D Telephone No. +49 89 2399 7413

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/14119

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-94	as originally filed			

Claims, No.:

1-5,14-35,44-62	as originally filed			
6-13,36-43	as received on	09/10/2000	with letter of	05/10/2000

Drawings, sheets:

1/5-5/5	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been stablished as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-10,13,14,25-29,32,33(in full); 1-5,11,12,15-45,47-62(in part).

because:

☒ the said international application, or the said claims Nos. 20-38,40,42-45,47-62 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 6-10,13,14,25-29,32,33(in full); 1-5,11,12,15-24,30,31,34-45(in part).

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional f es under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	20-24,30,31,34-38,40-42,44-62
	No:	Claims	1-5,11,12,15-19,39,43
Inventive step (IS)	Yes:	Claims	47-62
	No:	Claims	1-5,11,12,15-24,30,31,34-46
Industrial applicability (IA)	Yes:	Claims	1-5,11,12,15-19,39,41,46
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the International application have been noted:

see separat sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/14119

VIII. Certain observations on th international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/US99/14119

Section II

1. There appears to be no basis for the subject-matter of claims 1-45 in the priority document of 23.06.98. Therefore, the valid priority date for said claims is the international filing date of 23.06.99.

Section III

2. Non-establishment of opinion

a. For claims 1-45, examination has been restricted to those parts of the claimed subject-matter for which a search has been established (Rule 66.1(e) PCT), as defined in the International Search Report: this is limited to aspects relating only to viral proteases of HIV. Claims 6-10, 13, 14, 25-29, 32 and 33 specifically relate to different subject-matter, so that no opinion is provided for these claims. Furthermore, claims 1-5, 11, 12, 15-24, 30, 31 and 34-45 have a wider scope than that searched, and therefore have been examined only in part.

b. Claims 20-38, 40, 42-45 and 47-62 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section IV

3. Lack of unity of invention

a. The application lacks unity within the meaning of Rule 13.1 PCT. Independent claim 1 is directed to an assay for determining the biochemical fitness of a biochemical target of a mutant biological entity relative to its predecessor, in the presence of an inhibitor; the higher the fitness of the mutant target, the greater is the selection pressure for the mutation to arise. Similarly, claim 20, although directed to a method of administering a compound, relates to a method in which the relative biochemical fitness of a biochemical target in a biological entity and a mutant form thereof are determined in the presence of a plurality of potential

inhibitors; the inhibitor which produces the lowest biochemical fitness in the mutant is then administered as a therapeutic. Claim 46 provides a method of measuring specifically anti-HIV protease activity of an inhibitor. Claim 47 provides a method of preventing development of drug resistance in an HIV-infected mammal by administration of a compound having the given formula, in the presence of which a mutant HIV has lower fitness than the non-mutant form.

b. Thus, claims 1, 20 and 46 provide methods by which the evolutionary response of biochemical targets to inhibitors thereof can be assessed in terms of the likelihood of the target mutating to a drug-resistant form, whereas claim 47 provides a method using compounds which are known inhibitors of HIV protease mutants, and which therefore reduce the selection pressure for mutation. The only link between claim 47 and claims 1, 20 and 46 is the general teaching that inhibitors which are more active against a mutant form of the target than its predecessor will inhibit incidence of mutation and therefore reduce drug-resistance. This teaching is not novel, even when applied to the specific case with HIV proteases, inhibitors thereof, and drug-resistance thereto (see D1: abstract; col.12 l.8-12; claims 20-24; D2: abstract and methods). Thus, the subject-matters of these independent claims are not so linked as to form a single general inventive concept (Rule 13.1 PCT).

c. Therefore, the separate groups of invention are:

Invention I: Assays comprising determining the evolutionary response of a biochemical target to an inhibitor thereof, and for measuring anti-HIV protease activity of an inhibitor (Claims 1-46);

Invention II: Method of preventing development of drug-resistance in HIV-infected mammal by administering compounds which are known to inhibit development of drug resistance (Claims 47-62).

Section V

4. It is stressed that examination with respect to novelty, inventive step and industrial applicability refers only to matter for which an international search has been carried out (see Section III).

5. The applicant's observations submitted with the amend d claims have been considered in establishing this report.

6. Reference is made to the following documents:

D1: US-A-5 766 842 (Sepracor Inc.; 16.06.98);
D2: Klabe et al., Biochemistry, Vol.37, pp.8735-8742 (1998);
D3: Borman et al., J.Gen.Virol., Vol.77, pp.419-426 (1996);
D4: WO-A-95 06030 (G.D.Searle & Co. and Monsanto Co.; 02.03.95).

7. Novelty (Article 33(2) PCT)

a. Claim 1 is directed to an assay for determining the biochemical fitness of a biochemical target of a mutant replicating biological entity relative to its predecessor. The method comprises determining the ability of the target in the mutant to perform its function in the presence of an inhibitor (the so-called "vitality") and comparing this with the vitality of the target of the predecessor.

b. D1 discloses methods of identifying drug-resistant, biologically active mutants of a protein that may emerge in response to a drug targeted thereto, with particular reference to HIV protease (abstract). The term "drug-resistant" in this respect refers to mutant proteins which maintain significant levels of activity or function in the presence of concentrations of a drug sufficient to inactivate or inhibit the function of wild-type protein (col.12, l.8-12). Thus, resistance through mutation is assessed according to activity relative to the unmutated form ("predecessor", as termed in the present application). Resistance may be determined with respect to the activity of HIV-1 protease (such as in D1: claims 20-24). Although the method of D1 appears to concentrate on determining the numbers of mutants isolated (e.g. claim 21(d)), it still requires that each of the potentially resistant mutations is assessed for its ability to function in the presence of the inhibitor, relative to that of the wild-type. Thus, present claim 1 is not distinguished from the method of D1, which consequently falls within the scope of present claim 1 as well as that of claims 2-5, 11, 12, 15 and 39. Therefore, said claims appear to be not novel.

c. D2 relates to resistance to HIV protease inhibitors and discloses a comparison of

enzyme inhibition and antiviral potency, in which an enzymatic assay and a whole-cell viral infectivity assay were used to measure the inhibition constants for wild-type and mutant HIV proteases and viruses. Enzyme resistance to HIV protease inhibitors was determined by measuring the change in dissociation constants (or Kd values, used to represent Ki values) for each of 5 active site mutations compared to the wild-type (abstract, line 4; p.8736, col.1, 2nd full paragraph). Vitality values were calculated as shown (p.8736, col.1, 3rd full paragraph). Regardless of the outcome of the experiments and any indications which may be provided as to the value of the methods as used in D2, the methods as defined in claims 1-5, 11, 12, 15-19, 39 and 43 are not distinguished from those in D2, and are therefore not novel.

8. Inventive step (Article 33(3) PCT)

a. Present claim 20 differs from D2 in that, having determined the biochemical fitness of HIV-protease in the presence of at least two compounds, the compound that produces the lowest said fitness is administered as a therapeutic inhibitor of the protease. D2 does not disclose such a direct approach; it is pointed out (D2: p.8741, "Conclusions") that such an assay as used may suffice to discover potent inhibitors, but that quantitative structural activity relationships of inhibitors to HIV protease mutations require both an enzyme and a virally-based assay. Therefore, D2 does not teach against the use of such enzyme-based assays, but advocates their application in conjunction with a virally based assay. Thus, it is considered that having used an assay of biochemical fitness to discover potent inhibitors, the skilled person would be motivated to administer the inhibitors therapeutically, even if only in further testing. Therefore, the subject-matter of claim 20 and dependent claims 21-24, 30, 31, 34-38 and 40 appears not to involve an inventive step.

b. Dependent claims 41, 42, 44 and 45 do not appear to contain any additional features which, in combination with the features of the claims to which they refer, would render them inventive in the sense of Article 33(3) PCT: as pointed out in D3 (abstract), the selection of HIV-1 variants resistant to protease inhibitors is a gradual process during which mutations accumulate at different sites in the protease, generating virus populations with increasing resistance to the drug. Therefore, the skilled person would be well aware of the importance of relating

anti-protease activity not just to the wild-type, but also to strains which may already have some degree of resistance.

c. Claim 46, relating to a continuous fluorogenic assay for measuring anti-HIV protease activity of a protease inhibitor, appears not to be inventive. In D2 is described an assay (p.8736, col.2 - p.8738, col.1 "HIV Protease Assays"), in which the activity is measured in the absence and presence of inhibitor. According to this method, HIV protease is preincubated with inhibitor, and then substrate (2-aminobenzoyl-ATHQVYF(NO2)VRKA-OH: see "Substrate" p.8736, col.2) is added; after incubation and termination, products are separated by ion-exchange HPLC, and the fluorescent cleavage product measured. The reaction velocities in the absence and presence of inhibitor are determined and used to calculate protease activity and inhibition thereof.

The method of claim 46 differs from that in D2 in that it uses a different substrate, and different mathematical handling of the data. However, these features do not form a basis for an inventive step as they appear to represent standard alternatives: the substrate appears to be known for such assays (see description, p.74, l.17-20), and the data handling uses known methods in the art (p.75, l.15-21). Therefore, the subject-matter of claim 46 is not inventive.

9. Claim 47 is directed to a method of preventing the development of drug resistance in an HIV-infected mammal, comprising administering an effective amount of a compound of the given formula. Although compounds falling within the scope of the formula are known from the prior art as inhibitors of HIV protease (compare D4: abstract and p.202 and 204 with present claims 53-59), there is no prior disclosure to the effect that such compounds act against selective pressure, thereby reducing the risk of drug-resistant mutations arising. Therefore, claim 47 and dependent claims 48-62 appear to be novel and inventive.

10. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 20-38, 40, 42-45 and 47-62 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the

formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VII

11. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

Section VIII

12. The following points are according to Article 6 PCT:

a. As noted in the ISR, the scope of claims 1-45 is not supported by the description, as their scope is much broader than the description and drawings. The specification reserves all discussion to the case of drug resistance of HIV, and provides no examples or discussion of other aspects of the presently claimed invention, for instance with respect to bacteria. It is not considered sufficient support simply to provide a list of organisms to which the invention may be applied, as on p.22, l.24 - p.23, l.31.

b. The vague and imprecise statement in the description, referring to the "spirit" of the invention (bridging paragraph, page 93-94) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity when used to interpret them (see also PCT Guidelines, C-III, 4.3a).